BG cont SUB C15 cont

reactive with a CD28 receptor to bind the CD28 receptor and inhibit the production of the cytokine by the T cells.--

REMARKS

Claims 1-76 are pending. Claims 67-76 have been withdrawn as directed to a non-elected invention. Claims 2, 16, 43-46, 50 and 58 have been canceled hereinabove. Claims 1, 3, 15, 18, 21, 35, 47, 51, and 52 have been amended hereinabove. Accordingly, claims 1, 3-15, 17-42, 47-49, 51-57, and 59-66 are presently being examined.

Applicants maintain that the amendments to the claims do not raise an issue of new matter. Support for the amendment to the claims may be found in the specification and claims as originally filed as follows:

Amendment to claim 1: originally filed claim 1; page 7, line 11; and page 23, lines 33-35

Amendment to claim 3: originally filed claim 3; page 7, line 11.

Amendment to claim 15: originally filed claim 15 and 16.

Amendment to claim 18: originally filed claim 18; page 7, line 11.

Amendment to claim 21: originally filed claim 21.

Amendment to claim 35: originally filed claim 35; page 7, lines 5-13; and page 21, lines 17-26

Amendment to claim 47: originally filed claim 47.

Amendment to claim 51: originally filed claim 51.

Amendment to claim 52: originally filed claim 52; page 24, lines 15-16.

New claim 77: originally filed claim 45.

In view of the preceding amendments and the remarks which follow, applicants respectfully request that the Examiner enter the amendments to the claims.

Moreover, in view of the changes hereinabove and the following comments, applicants respectfully request that the Examiner reconsider and withdraw the various grounds for objection and rejection set forth in the March 25, 1992 Office Action.

At page 2 of the March 25 Office Action, the Examiner acknowledged applicants' election of Group I, i.e. claims 1-62, with traverse, for prosecution at this time. The Examiner was partially persuaded by applicants' traversal and has included claims 63-66 as part of Group I. Accordingly, claims 1-66 have been examined together. However, the Examiner has taken the position that claims 67-76 have been properly restricted, and thus has made the requirement final.

Further, the Examiner encouraged applicants to file an Information Disclosure Statement, including PTO Form 1449. Applicants' wish to point out to the Examiner that an Information Disclosure Statement was submitted on June 2, 1992 in compliance with 37 C.F.R. § 1.97 through 1.99. Acknowledgement is respectfully requested.

APPLICANTS' INVENTION

Before addressing the specific objections and rejections set forth

in the March 25, 1992 Office Action, applicants wish to emphasize that their claimed invention relates to the totally unexpected discovery of a method for regulating functional T cell responses comprising contacting CD28 positive T cells with a B7 antigen thereby regulating functional T cell responses.

The data set forth in Exhibit 1 (provided hereinafter) clearly shows that one can manipulate the mouse immune system into accepting transplanted tissue instead of attacking it by blocking the binding of the B7 antigen to the CD28 receptor such that the B7 antigen does not bind to the CD28 receptor and the transplanted tissue is tolerated by the body.

This invention also provides a B7Ig fusion protein reactive with the CD28 receptor on T cells. This fusion protein comprises a polypeptide having (1) a first amino acid sequence containing amino acid residues from about position 1 to about position 215 of the amino acid sequence encoding the extracellular domain of B7 antigen and (2) a second amino acid sequence corresponding to the hinge, CH2 and CH3 regions of human immunoglobulin Cgamma1. In one embodiment, the B7Ig fusion protein corresponds to the amino acid sequence encoded by DNA having ATCC No. 68627.

This invention further provides a monoclonal antibody reactive with the fusion protein described hereinabove.

Additionally, this invention provides a CD28Ig fusion protein reactive with the B7 antigen. This fusion protein comprises a polypeptide having (1) a first amino acid sequence containing amino acid residues from about position 1 to about position 134 of the amino acid sequence corresponding to the extracellular domain of CD28 receptor and (2) a second amino acid sequence corresponding to the hinge, CH2 and CH3 regions of human immunoglobulin Cgamma1. In

one embodiment, the CD28Ig fusion protein corresponds to the amino acid sequence encoded by DNA having ATCC No. 68628.

This invention also provides a method for preventing the binding of the CD28 receptor to the B7 antigen so as to inhibit functional T cell responses comprising contacting CD28 positive T cells with an anti-CD28 monoclonal antibody which recognizes and binds to the CD28 receptor so as to prevent binding of said receptor to the B7 antigen.

Additionally, the claimed invention includes a method for treating immune system diseases mediated by CD28 positive T cell interactions with B7 positive cells comprising administering to a subject a ligand for CD28 receptor to regulate the functional T cell response and/or to regulate cytokine levels.

Also, the claimed invention provides a method for treating cancer associated with expression of B7 antigen in vivo comprising administering to a subject a ligand reactive with the B7 antigen.

Further, the claimed invention also provides a method for inhibiting T cell proliferation in graft versus host disease comprising contacting T cells with a ligand for CD28 receptor and an immunosuppressant.

REJECTION UNDER 35 U.S.C. §101

The Examiner rejected claims 1-66 under 35 U.S.C. § 101. The Examiner alleged that the specification fails to adequately teach how to use the claimed B7 antigen protein/fusion protein, CD28 protein/fusion protein and monoclonal antibodies, in compositions to achieve an in vivo therapeutic [effect] which would regulate T-cell response.

The Examiner noted that the claimed invention is supported only by in vitro data, particularly with regard to claims directed to regulating T-cell responses, treating cancer, lymphoma, leukemia, and graft versus host disease. The Examiner alleges that applicants have made no showing that the data provided in the subject application correlate with utility for in vivo therapy in humans. Further, the Examiner alleged that in vitro data, such as that reported in the subject application, and animal model studies frequently do not correlate with clinical utility in in vivo patient trials.

The Examiner has taken the position that based on the evidence of record, the alleged utility of the claimed compositions for the regulation of T cell responses would not be believable on its face to the person of skill in the art in view of the contemporary knowledge in the art. The Examiner stated that the applicants have not provided any showing of therapeutic utility of the subject or of the claimed compositions which would lead one of skill in the art to believe that the antibody is broadly applicable for the regulation of T cell responses in humans.

Applicants respectfully traverse the Examiner's position for the following reasons.

Applicants provide in vivo data in mouse showing that blocking the CD28 receptor from binding the B7 antigen results in manipulating the mouse immune system into accepting transplanted tissue instead of attacking it and thereby preventing the rejection of transplanted tissue (see Figures 1-4 of D. Lenschow et al. (1992) Science 257:789-792 entitled "Long Term Survival of Xenogeneic Pancreatic Islet Grafts Induced by CTLA4Ig" annexed hereto as Exhibit 1). Applicants point out that Drs. Linsley and Brady, co-inventors of the subject invention, were co-authors in this paper.

Specifically, Lenschow et al. in Figure 3 shows that animals which were transplanted and then treated with 50 micrograms of monoclonal antibody to human B7 every day for 14 days after transplant exhibited prolonged graft survival over control animals (9 to>50 days) (Lenschow at page 790, right column, last paragraph and page 791, left column, first paragraph and Figure 3, legend). Lenschow et al. concludes that blocking the interaction of co-stimulatory molecules such as CD28-B7 may provide a new approach to immunosuppression (Lenschow at page 792, left column, last sentence).

In view of the in vivo data as shown in Exhibit 1, applicants respectfully contend that contrary to the Examiner's position in vitro data correlates with utility in vivo and thus the Examiner's rejection under 35 U.S.C. §101 has been overcome.

In any event, applicants respectfully point out that in vitro results with respect to the particular pharmacological activity are generally predictive of in vivo test result, i.e. there is a correlation therebetween (Cross v. Iizuka, 224 USPQ 739, 747 (CAFC 1989)). Were this not so, the testing procedures of the pharmaceutical industry would not be as they are (Id.).

For the reasons discussed hereinabove, applicants request that the Examiner reconsider and withdraw this rejection.

REJECTION UNDER 35 U.S.C. §112, FIRST PARAGRAPH

At page 3 of the March 25 Office Action, the Examiner objected to the specification under 35 U.S.C. § 112, first paragraph, as allegedly failing to provide an adequate written description of the

claimed invention and for failing to adequately teach how to make and use the claimed invention, i.e. failing to provide an enabling disclosure.

Specifically the Examiner alleged that applicants have not disclosed to one of ordinary skill in the art how to use the protein as a pharmaceutical or therapeutic agent. Allegedly, there is an insufficient written description of the invention with respect to the in vivo operability of the protein to enable one of ordinary skill in the art to use applicants' invention for the reasons discussed hereinabove.

Further, the Examiner alleged that applicants have not provided any guidance indicating what dosages are required and the ways the protein may be administered to a subject or otherwise used in a practical manner. Therefore, the Examiner has taken the position that it would require undue experimentation of one of ordinary skill in the art to determine how to use the claimed protein for the reasons previously discussed.

The Examiner noted applicants' reference to deposits but stated that they are insufficient assurances that all required deposits have been made and all conditions of MPEP §608.01 (p)(c) have been met. Further, the Examiner is requiring applicants to deposit monoclonal antibodies which recognize the claimed proteins.

At page 4 of the March 25 Office Action, the Examiner rejected claims 1-66 under 35 U.S.C. § 112, first paragraph for the reasons set forth in the objection to the specification.

In response to the Examiner's objection, applicants point out that in vivo mouse studies show that when the CD28 receptor is blocked from binding the B7 antigen it results in preventing the rejection

of transplanted tissue as stated hereinabove and shown in Exhibit 1.

Additionally, applicants respectfully contend that the dosage of the claimed proteins would vary with various factors such as the type of subject (e.g. its height and weight), the purpose of the treatment, the mode of administration and the like, and the determination of such factors would be well within the skill of one skilled in the art. Further, applicants contend that it would be well within one having ordinary skill in the art to know that the claimed proteins may be administered to a host subject in a variety of routes including injection intratumorally, intravenously, intraarterially, subcutaneously, or intramuscularly.

In response to the Examiner's statement that there is insufficient assurances that all required deposits have been made, applicants respectfully point out that the claimed invention is directed to fusion proteins and methods for regulating the T cell response. Accordingly, applicants contend that the deposit of DNA encoding such fusion proteins teaches a person having ordinary skill in the art to which the subject pertains how to make and use the claimed invention in accordance with 35 U.S.C. §112.

Moreover, applicants maintain that the DNA that encodes the claimed fusion proteins (i.e. the DNA encoding the amino acid sequence corresponding to the B7Ig fusion protein designated ATCC No. 68627 and the DNA encoding the amino acid sequence corresponding to the CD28Ig fusion protein designated ATCC No. 68628) have been deposited pursuant to the Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure with the Patent Culture Depository of the American Type Culture Collection (ATCC), 12301 Parklawn Drive, Rockville, Maryland 20856 U.S.A.

Applicants maintain that during the pendency of the subject application, access to the ATCC deposits will be afforded to one determined by the Commissioner to be entitled thereto under 35 U.S.C. §1.14 and §122, and all restrictions on the availability to the public of the material deposited under ATCC Accession Nos. 68627 and 68628 will be irrevocably removed upon the issuance of a patent from the subject application. Furthermore, the above deposits will be maintained by the ATCC for a period of 30 years from the date of deposit or at least 5 years after the last request for a sample of the deposited material, whichever is longer. Where the ATCC cannot furnish samples of the above deposits for any reason, applicants shall make a replacement deposit, of the material which was originally deposited, within three months of receiving notification that the ATCC cannot furnish samples. All restrictions on the availability to the public of the deposited cell lines will be irrevocably removed upon the granting of a patent of the subject application.

In view of applicants' preceding comments applicants request that the Examiner reconsider and withdraw these objections to the specification.

Further, for the same reasons, applicants request that the Examiner reconsider and withdraw the rejection under 35 U.S.C. §112, first paragraph, based upon the foregoing objections to the specification.

Additionally, the Examiner rejected claims 1-66 under 35 U.S.C. § 112, first paragraph. Allegedly, the disclosure is enabling only for claims limited to <u>in vitro</u> regulation of T-cell responses.

Applicants respectfully contend that the disclosure is enabling for claims generally directed to regulation of T cell responses as recited in the claims for the reasons stated hereinabove.

REJECTION UNDER 35 U.S.C. §112, SECOND PARAGRAPH

The Examiner rejected claims 15, 16, and 21 under 35 U.S.C. § 112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim a subject matter which applicants regard as the invention.

Specifically, the Examiner alleged that claims 15 and 16 are indefinite by reciting the term "anti-CD." Allegedly, the term "anti-CD" is nondescriptive. Therefore, the Examiner is puzzled as to what the term "anti-CD" refers to. The Examiner noted that the term may represent a particular CD antigen; however, the exact antigen is unknown. The Examiner stated that if "anti-CD" refers to a particular CD antibody, the exact antigens must be incorporated into the claim language, e.g. anti-CD3 antibody. As a result, the Examiner is requiring applicants to amend the claims to definitively identify the subject matter being claimed.

The Examiner also alleged that claim 21 is indefinite in the use of the period after antigen on the second line of the claim. The Examiner is puzzled whether the claim was intended to end with this period or include the third line. Therefore, the Examiner is requiring applicants to amend claim 21 accordingly.

In accordance with the Examiner's suggestion applicants have (1) amended claim 15 to recite "The method of claim 1 further comprising adding anti-CD2 or anti-CD3 antibody to co-react with said T cells;" (2) canceled claim 16; and (3) amended claim 21 to recite "The method of claim 19, wherein the ligand is a Fab

fragment of a monoclonal antibody reactive with B7 antigen and the T cell responses are inhibited."

In view of these changes, applicants respectfully request that the Examiner reconsider and withdraw the rejection.

REJECTION UNDER 35 U.S.C. §102(b)/103

At page 6 of the March 25 Office Action, the Examiner rejected claims 1, 15, 16, 35-40, 43-45, 50-52, 55, 56, 58, 59, 60, 63, and 66 under 35 U.S.C. § 102(b) as allegedly anticipated by or, in the alternative, under 35 U.S.C. § 103 as allegedly obvious over Damle et al.

Damle et al. allegedly teaches that the CD28 molecule is expressed on the surface of a majority of human T-cells and has been implicated to play an active role in the regulation of T-cell growth. The Examiner stated that Damle et al. teach using an anti-CD28 antibody alone or in combination with anti-CD3 antibody thereby showing its affect on T-cell stimulation and cytokine induction.

Allegedly, the anti-CD28 antibody would inherently inhibit, like claim 55, or stimulate, like claim 56, functional T-cell responses including the production of cytokines, which include interleukins, interferons, transforming growth factors, TNF and CSF.

The Examiner stated that Damle et al. incorporate by reference the teachings of Martin et al. The Examiner further stated that Martin et al. teach the monoclonal antibody 9.3. Allegedly, this monoclonal antibody will inherently recognize the CD28 receptor as a membrane protein or as a soluble fusion protein. The Examiner has taken the position that methods of producing proteolytic

antibody fragments were well known in the art at the time the invention was made. Allegedly, it is clear in the art that antibodies to cell adhesion molecules can inhibit T-cell activation and therefore are potentially important in immune system diseases including cancers such as T-cell leukemias and graft host disease. Further, the Examiner stated that the drug cyclosporine was well known as an immunosuppressant prior to the date of applicants' invention.

Applicants respectfully traverse the Examiner's position for the following reasons.

The claimed invention, as amended, includes a method for regulating functional T cell responses comprising contacting CD28 positive T cells with a B7 antigen thereby regulating functional T cell responses. In contrast, Damle teaches that the anti-CD28 monoclonal antibody in its intact form or its F(ab')2 fragments had a strong growth-promoting effect on both anti-CD3-induced and IL-2 induced proliferation (Damle at page 1758, second column, second full paragraph, lines 14-17). Additionally, Damle et al. teaches that anti-CD28 mAb not only inhibited proliferation of T cells in allogeneic mixed lymphocyte reaction (hereinafter referred to as "MLR") but also their subsequent differentiation into cytotoxic T lymphocytes (hereinafter referred to as "CTL") (Damle at page 1758, second column, second full paragraph, lines 17-21).

However, Damle et al. do not specifically teach contacting CD28 positive T cells <u>with a B7 antigen</u>. A critical advantage of the claimed invention is the realization of the fact that the B7 antigen specifically interacts with CD28 receptor. Applicants respectfully contend that a reference that does not teach this fact cannot anticipate the claimed invention or make it obvious. Therefore, the Damle reference does not and cannot anticipate the

claimed method.

Additionally, the claimed invention, as amended, includes a method for preventing the binding of the B7 antigen to the CD28 receptor comprising contacting CD28 positive T cells with an anti-CD28 monoclonal antibody which recognizes and binds to the CD28 receptor so as to prevent binding of said receptor to the B7 antigen.

In contrast, Damle merely teaches that the inhibitory effect of anti-CD28 mAb on the development of CTL in the MLR could be due to the inhibition of clonal expansion (proliferation) of CD8+CD28+ precursors of CTL in addition to that of CD4+CD28+helper/inducer cells that provide the necessary growth- and differentiation-inducing factors such as IL-2 (Damle et al at page 1755, second column, second full paragraph, last sentence). Damle did not teach or suggest the interaction of the B7 antigen with the CD28 molecule. Therefore, the Damle reference does not anticipate the claimed invention.

Additionally, the claimed invention includes a method for treating a subject with an immune system disease[s] mediated by CD28 positive T cell interactions with B7 positive cells comprising administering to the subject a ligand for CD28 receptor to regulate the functional T cell response and/or to regulate cytokine levels and a pharmaceutically acceptable carrier. In contrast, Damle merely discloses that anti-CD28 mAbs may exert either stimulatory or inhibitory effects on T cells, depending, in part, on the degree of crosslinking or "aggregation" of the CD28 receptor (Damle at page 1759, second column, first paragraph, penultimate sentence).

However, the Damle reference does not disclose or suggest the advantage of mediating CD28 positive T cell interactions with B7 positive cells let alone a method for treating immune system

diseases thereby. Therefore, the Damle reference cannot anticipate the claimed invention.

In view of the foregoing comments, applicants request that the Examiner reconsider and withdraw her rejections of claims 1-17 and 22-55 under 35 U.S.C. §102(b).

In the alternative, the Examiner rejected claims 1-17 and 22-55 under 35 U.S.C. §103 as allegedly unpatentable over Damle et al.

Applicants respectfully traverse the Examiner's position. The Damle reference does not suggest the claimed invention, as amended, for the following reasons.

As stated hereinabove, the claimed invention, as amended, includes a method for regulating functional T cell responses comprising contacting CD28 positive T cells with a B7 antigen thereby regulating functional T cell responses.

Damle et al. has been previously discussed.

Applicants once again state that Damle et al. do not teach contacting CD28 positive T cells with a B7 antigen. Moreover, in accordance with the Examiner's statement "Damle et al. do not specifically teach the use of antibody as a method of regulating T cell response" (Office Action at paragraph 31, page 7). Applicants respectfully contend that because a critical advantage of the claimed invention is the realization of the fact that the B7 antigen specifically interacts with the CD28 receptor and because the Damle reference does not suggest this fact, the Damle reference does not suggest the claimed method.

Additionally, the claimed invention, as amended, includes a method

for preventing the binding of the B7 antigen to the CD28 receptor comprising contacting CD28 positive T cells with an anti-CD28 monoclonal antibody which recognizes and binds to the CD28 receptor so as to prevent binding of said receptor to the B7 antigen.

In contrast to the claimed invention, Damle et al. did not teach or suggest the interaction of the B7 antigen with the CD28 molecule and thus could not have suggested the utility for preventing the binding of the B7 molecule to the CD28 receptor as claimed. Therefore, the Damle reference does not suggest the claimed invention.

Additionally, the claimed invention includes a method for treating a subject with an immune system disease mediated by CD28 positive T cell interactions with B7 positive cells comprising administering to the subject a ligand for CD28 receptor to regulate the functional T cell response and a pharmaceutically acceptable carrier.

In contrast to the claimed invention, Damle et al. do not disclose that mediating CD28 positive T cell interactions with B7 positive cells would regulate the T cell response. In accordance with the Examiner's statement "Damle et al. do not specifically teach the use of antibody as a method of regulating T cell response." For these reasons, applicants respectfully contend that the Damle reference does not suggest the claimed invention.

Further, applicants submit that since Damle does not teach or suggest blocking the binding of the CD28 receptor from binding the B7 antigen in order to practice the claimed method, the Examiner's assertion of obviousness is not well taken. Accordingly, for the reasons provided hereinabove, applicants assert that the Damle references does not render the subject invention obvious.

Applicants contend that the Examiner's statement that "it is clear in the art the antibodies to cell adhesion molecules can inhibit T-cell activation and therefore are potentially important in treating immune system diseases, including cancers such as T-cell leukemias and graft versus host disease" is "hindsight reconstruction of the claimed invention." In accordance with the Examiner's statement "Damle et al. do not specifically teach the use of antibody as a method of regulating T cell response" let alone that the use of such antibody would be useful to treat subjects suffering from an immune disease.

Moreover, although it is true that cyclosporin has been extensively used to prevent organ rejection, applicants contend that the claimed methods are not directed to using cyclosporin. Instead, the claimed invention is directed to a method for inhibiting T cell proliferation in graft versus host disease comprising contacting T cells with a ligand for CD28 receptor and an immunosuppressant. It is the result of using the combination of the ligand for CD28 receptor and the immunosuppressant which inhibits T cell proliferation. In contrast to the claimed invention, Damle et al. did not suggest the use of such a combination. Therefore, Damle et al. do not render obvious the claimed invention.

In view of applicants' preceding comments applicants request that the Examiner reconsider and withdraw these rejections to the claims.

PROVISIONAL REJECTION UNDER 35 U.S.C. §103

Additionally, at page 6 of the March 25 Office Action, the Examiner provisionally rejected claims 1-66 under 35 U.S.C. § 103 as allegedly obvious over co-pending application U.S. Serial No. 547,980. The Examiner stated that this co-pending application

has a common inventor with the subject application. The Examiner stated that based upon the earlier effective U.S. filing date of the co-pending application, it would constitute prior art under 35 U.S.C. § 102(e) if patented. The Examiner indicated that this provisional rejection under 35 U.S.C. § 103 is based upon a presumption of future patenting of the conflicting application.

In response to the Examiner's statements, applicants point out that co-pending U.S. Serial No. 547,980, filed January 24, 1991 will be abandoned. Therefore, the Examiner's rejection of claims 1-66 under 35 U.S.C. §103 will be rendered moot.

For these reasons, applicants respectfully request that the Examiner reconsider and withdraw the rejection under 35 U.S.C. § 103.

REJECTION UNDER 35 U.S.C. §103, DOUBLE PATENTING

Also, at page 6 of the March 25 Office Action, the Examiner provisionally rejected claims 1-66 under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 1-29 of co-pending U.S. Serial No. 547,980. The Examiner noted that although the conflicting claims are not identical, they are not patentably distinct from each other because they each are directed to a method of regulating T-cell responses by modulating the interaction between CD28 and the B7 antigen.

Once again applicants point out that co-pending U.S. Serial No. 547,980, filed January 24, 1991 will be abandoned. Therefore, the Examiner's rejection of claims 1-66 under 35 U.S.C. §103 will be rendered moot.

For these reasons, applicants respectfully request that the Examiner reconsider and withdraw the rejection under 35 U.S.C. § 103.

REJECTION UNDER 35 U.S.C. §103

Additionally, at page 7 of the March 25 Office Action, the Examiner rejected claims 1, 15, 16, 35-40, 43-45, 50-52, 55, 56, 58, 59, 60, 63, and 66 under 35 U.S.C. §103 as allegedly unpatentable over Damle et al.

Allegedly, Damle et al. teach that the CD28 molecule is expressed on the surface of a majority of human T-cells and has been implicated to play an active role in the regulation of T-cell growth. The Examiner noted that Damle et al. used an anti-CD28 alone and in combination with anti-CD3 antibodies to use its affect on T-cell stimulation and Cytokine induction. Allegedly, Damle et al. incorporate by reference the teachings of Martin et al.

The Examiner stated that Martin et al. teach the monoclonal antibody 9.3. The Examiner further stated that Damle et al. do not specifically teach the use of the antibody as a method of regulating T-cell responses. However, since the antibody is the same as that of Martin et al. and in considering the contemporary knowledge in the art at the time the invention was made, the Examiner has taken the position that it would have been prima facie obvious to a person of ordinary skill in the art to use the CD28 antibody as a method of regulating T-cell responses.

The Examiner further stated that this antibody would inherently inhibit, as recited in claim 55, or stimulate, as recited in claim 56, functional T-cell responses including the production of Cytokines which include interleukins, interferons, transforming

growth factors such as TNF and CSF. The Examiner alleged that the monoclonal antibody will inherently recognize the CD28 receptor as a membrane protein or as a soluble fusion protein.

The Examiner has further taken the position that methods of producing proteolytic antibody fragments were well known in the art at the time the invention was made. The Examiner stated that it is clear in the art the antibodies to cell adhesion molecules can inhibit T-cell activation and therefore are potentially important in treating immune system diseases, including cancers such as T-cell leukemias and graft versus host disease. Allegedly, the drug cyclosporine was well known as an immunosuppressant prior to the date of applicants' invention.

Applicants respectfully traverse the Examiner's rejection of the claims under 35 U.S.C. §103 for the reasons provided hereinabove beginning at the middle of page 17 and respectfully request that the Examiner reconsider and withdraw the rejection under 35 U.S.C. §103.

Applicants acknowledge that the following references have been made of record but are not relied upon:

1. Freeman, et al. (1987) J. Immunology 139:3260-3267;
2. Freeman, et al. (1989) J. Immunology 143:2716-2722;
3. Martin, et al. (1986) J. Immunology 136:3282-3287.

Because of the preceding discussion, cancellations, and amendments, applicants request that the Examiner reconsider and withdraw the various grounds for objection and rejection set forth in the March 25, 1992 Office Action and earnestly solicit allowance of the claims now being examined.

If a telephone interview would be of assistance in advancing

prosecution of the subject application, applicants' undersigned attorney invites the Examiner to telephone her at the number provided below.

No fee, other than the $350.00 fee for a two month extension of time (a check for which is enclosed), is deemed necessary in connection with the filing of this Amendment. However, if any additional fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 19-2090.

Respectfully submitted,

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I hereby certify that this paper is being deposited this date with the U.S. Postal Service as first class mail addressed to: Commissioner of Patents and Trademarks, Washington, D.C. 20231.

Marilyn Bass 8/24/92
Signature Date